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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **DIAGNOSTICS AND THERAPEUTICS FOR DISEASES ASSOCIATED WITH PHOSPHODIESTERASE 1B (PDE1B)**

(57) Abstract: The invention provides a human PDE1B which is associated with the cardiovascular disorders, metabolic diseases, gastrointestinal and liver diseases, cancer disorders, hematological disorders, respiratory diseases, neurological disorders and urological disorders. The invention also provides assays for the identification of compounds useful in the treatment or prevention of cardiovascular disorders, metabolic diseases, gastrointestinal and liver diseases, cancer disorders, hematological disorders, respiratory diseases, neurological disorders and urological disorders. The invention also features compounds which bind to and/or activate or inhibit the activity of PDE1B as well as pharmaceutical compositions comprising such compounds.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/002065

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 G01N33/68 G01N33/574 C12Q1/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
 EPO-Internal, BIOSIS, PAJ, WPI Data, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 085 092 A (PFIZER LTD ; PFIZER (US)) 21 March 2001 (2001-03-21) paragraph [0248] - paragraph [0330]; claims 9,11,12	1-25
P,X	WO 03/020702 A (CHILDRENS HOSP MEDICAL CENTER ; UNIV ROCKEFELLER (US)) 13 March 2003 (2003-03-13) page 16, line 24 - line 25; claims 5,19,27-33,53 page 44, last paragraph - page 45, paragraph 2	1-25
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

21 June 2004

Date of mailing of the international search report

25. 10. 2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002065

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRUUSE CHRISTINA ET AL: "The role of cGMP hydrolysing phosphodiesterases 1 and 5 in cerebral artery dilatation" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 420, no. 1, 18 May 2001 (2001-05-18), pages 55-65, XP002285171 ISSN: 0014-2999 page 64, last paragraph -----	19-21,24
X	US 6 372 777 B1 (MARTINS TIMOTHY J ET AL) 16 April 2002 (2002-04-16) column 10, line 8 - line 22 column 37, paragraph 4; claim 14 -----	19-21,24
X	US 5 885 834 A (EPSTEIN PAUL M) 23 March 1999 (1999-03-23) cited in the application claim 1 -----	19-21
X	JIANG XIN ET AL: "Inhibition of calmodulin-dependent phosphodiesterase induces apoptosis in human leukemic cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 93, no. 20, 1996, pages 11236-11241, XP002285172 ISSN: 0027-8424 cited in the application page 11240, column 2, last paragraph -----	19-21
A	YU JOSEPHINE ET AL: "Identification and characterisation of a human calmodulin-stimulated phosphodiesterase PDE1B1" CELLULAR SIGNALLING, vol. 9, no. 7, 1997, pages 519-529, XP002285173 ISSN: 0898-6568 cited in the application figure 5 -----	1-25
A	RYBALKIN SERGEI D ET AL: "Calmodulin-stimulated cyclic nucleotide phosphodiesterase (PDE1C) is induced in human arterial smooth muscle cells of the synthetic, proliferative phenotype" JOURNAL OF CLINICAL INVESTIGATION, vol. 100, no. 10, 15 November 1997 (1997-11-15), pages 2611-2621, XP002285174 ISSN: 0021-9738 page 2620, column 1, paragraph 4 - column 2, paragraph 2 ----- -/--	1-25

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002065

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KOSTIC M M ET AL: "Altered expression of PDE1 and PDE4 cyclic nucleotide phosphodiesterase isoforms in 7-oxo-prostacyclin-preconditioned rat heart"</p> <p>JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, XX, XX, vol. 29, no. 11, November 1997 (1997-11), pages 3135-3146, XP002278927</p> <p>ISSN: 0022-2828</p> <p>page 3144, column 1, line 9 - line 11</p> <p>-----</p>	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/002065

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: ²⁶
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 - 26 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 26

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are cardiovascular diseases.

2. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are metabolic diseases.

3. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are gastrointestinal diseases.

4. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are liver diseases.

5. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are cancer disorders.

6. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are hematological diseases.

7. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are respiratory diseases.

8. claims: 1-26[partially]

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are neurological disorders.

9. claims: 1-26[partially]

Diagnostics, therapeutics and methods of screening for therapeutics, relating to diseases associated with PDE1B, in which the diseases are urological diseases.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/002065

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1085092	A	21-03-2001	EP 1085092 A1	21-03-2001
			JP 2001149084 A	05-06-2001
WO 03020702	A	13-03-2003	CA 2459161 A1	13-03-2003
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